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Chapter

Varicella

VARICELLA IS AN ACUTE, CONTAGIOUS DISEASE CAUSED BY varicella zoster virus (VZV). The recurrent infection (herpes zoster, also known as shingles) has been recognized since ancient times. Primary varicella infection (chickenpox) was not reliably distinguished from smallpox until the end of the 19th century. In 1875, Steiner demonstrated that chickenpox was caused by an infectious agent by inoculating volunteers with the vesicular fluid from a patient with acute varicella. Clinical observations of the relationship between varicella and herpes zoster were made in 1888 by von Bokay, when susceptible children acquired varicella after contact with herpes zoster. VZV was isolated from vesicular fluid of both chickenpox and zoster lesions in cell culture by Thomas Weller in 1954. Subsequent laboratory studies of the virus led to the development of a live attenuated varicella vaccine in Japan in the 1970s. The vaccine was licensed for use in healthy children and adults in the United States in March 1995.

Varicella Zoster Virus (VZV)

VZV is a DNA virus, and is a member of the herpes virus group. Like other herpes viruses, VZV has the capacity to persist in the body after the primary (first) infection as a latent infection. VZV persists in sensory nerve ganglia. Primary infection with VZV results in chickenpox. Herpes zoster (shingles) is the result of recurrent infection. The virus has a short survival time outside the infected host.

Pathogenesis

VZV enters through the respiratory tract and conjunctiva. The virus is believed to replicate at the site of entry in the nasopharynx and in regional lymph nodes. A primary viremia occurs 4-6 days after infection, which disseminates the virus to other organs, such as the liver, spleen, and sensory ganglia. Further replication occurs in the viscera, followed by a secondary viremia, with viral

Varicella

- **Acute viral illness**
- **Zoster described in premedieval times**
- **Varicella not differentiated from smallpox until end of 19th century**
- **Infectious nature demonstrated in 1875**

Varicella Zoster Virus

- **Herpes virus (DNA)**
- **Primary infection results in varicella (chickenpox)**
- **Recurrent infection results in herpes zoster (shingles)**
- **Short survival in environment**

Varicella Pathogenesis

- **Respiratory transmission of virus**
- **Replication in nasopharynx and regional lymph nodes**
- **Repeated episodes of viremia**
- **Multiple tissues, including sensory ganglia, infected during viremia**

infection of the skin. Virus can be cultured from mononuclear cells of an infected person from 5 days before to 1 or 2 days following the appearance of the rash.

Varicella
Clinical Features

- **Mild prodrome (fever, malaise) for 1-2 days**
- **Successive crops (2-4 days) of pruritic vesicles**
- **Generally appear first on head; most concentrated on trunk**
- **Generally mild in healthy children**

Clinical Features

The **incubation period** is from 14 to 16 days from exposure, with a range of 10 to 21 days. This may be prolonged in immunocompromised patients and those who have received varicella zoster immune globulin (VZIG). The incubation period may be up to 28 days after VZIG.

Primary infection (chickenpox)

A mild **prodrome** may precede the onset of a rash. Adults may have 1 to 2 days of fever and malaise prior to rash onset, but in children the rash is often the first sign of disease.

The **rash** is generalized, pruritic, and rapidly progresses from macules to papules to vesicular lesions before crusting. The rash usually appears first on the scalp, moves to the trunk, and then the extremities, with the highest concentration of lesions on the trunk. Lesions also can occur on mucous membranes of the oropharynx, respiratory tract, vagina, conjunctiva, and the cornea. Lesions are usually 1 to 4 mm in diameter. The vesicles contain clear fluid on an erythematous base that may rupture or become purulent before they dry and crust. Successive crops appear over several days, with lesions present in several stages of evolution. For example, macular lesions may be observed in the same area of skin as mature vesicles. Healthy children usually have 200-500 lesions in 2 to 4 successive crops.

The **clinical course** in normal children is generally mild, with malaise, pruritus (itching), and fever up to 102°F for 2 to 3 days. Adults may have more severe disease and have a higher incidence of complications. Respiratory and gastrointestinal symptoms are absent. Children with lymphoma and leukemia may develop a severe progressive form of varicella characterized by high fever, extensive vesicular eruption, and high complication rates. Children infected with human immunodeficiency virus may also have severe, prolonged illness.

Recovery from primary varicella infection results in lifetime immunity. In otherwise healthy persons, clinical illness after reexposure is rare, but may occur, particularly in immunocompromised persons. As with other viral diseases, reexposure to natural (wild) varicella may lead to reinfection that boosts antibody titers without causing clinical illness or detectable viremia.

Recurrent disease (herpes zoster)

Herpes zoster, or shingles, occurs when latent VZV reactivates and causes recurrent disease. The immunologic mechanism that controls latency of VZV is not well understood. However, factors associated with recurrent disease include aging, immunosuppression, intrauterine exposure to VZV, and varicella at a young age (<18 months). In immunocompromised persons, zoster may disseminate, causing generalized skin lesions, and central nervous system, pulmonary, and hepatic involvement.

Herpes Zoster

- **Reactivation of varicella zoster virus**
- **Associated with:**
  - **aging**
  - **immunosuppression**
  - **intrauterine exposure**
  - **varicella at <18 month of age**

The vesicular eruption of zoster generally occurs unilaterally in the distribution of a dermatome supplied by a dorsal root or extramedullary cranial nerve sensory ganglion. Most often, this involves the trunk or the area of the fifth cranial nerve. Two to four days prior to the eruption there may be pain and paresthesia in the segment involved. There are few systemic symptoms. Post-herpetic neuralgia, or pain in the area of the recurrence which persists after the lesions have resolved, is a distressing complication of zoster, with no adequate therapy currently available. Post-herpetic neuralgia may last as long as a year after the episode of zoster. Ocular nerve and other organ involvement with zoster can occur, often with severe sequelae.

Complications

Acute varicella is generally mild and self-limited, but may be associated with complications. The most common complications of varicella include **secondary bacterial infections** of skin lesions, dehydration, pneumonia, and central nervous system involvement. Secondary bacterial infections of skin lesions with staphylococcus or streptococcus are the most common cause of hospitalization and outpatient medical visits. Secondary infection with invasive group A streptococci may cause serious illness and lead to hospitalization or death. **Pneumonia** following varicella is usually viral, but may be bacterial. Secondary bacterial pneumonia is more common in children <1 year of age. Up to 30% of pneumonia cases among healthy adults are fatal.

Varicella Complications

- **Bacterial infection of lesions**
- **CNS manifestations**
- **Pneumonia (rare in children)**
- **Hospitalization ~3 per 1000 cases**
- **Death ~ 1 per 60,000 cases**

Central nervous system manifestations of varicella range from aseptic meningitis to encephalitis. Involvement of the cerebellum, with resulting cerebellar ataxia, is the most common and generally has a good outcome. Encephalitis is an infrequent complication of varicella (estimated 1.8 per 10,000 cases), and may lead to seizures and coma. Diffuse cerebral involvement is more common in adults than in children.

Reye syndrome is an unusual complication of varicella and influenza and occurs almost exclusively in children who take aspirin during the acute illness. The etiology of Reye syndrome is unknown. There has been a dramatic decrease in the incidence of Reye syndrome during the past decade, presumably related to decreased use of aspirin by children.

Rare complications of varicella include aseptic meningitis, transverse myelitis, Guillain-Barre syndrome, thrombocytopenia, hemorrhagic varicella, purpura fulminans, glomerulonephritis, myocarditis, arthritis, orchitis, uveitis, iritis, and clinical hepatitis.

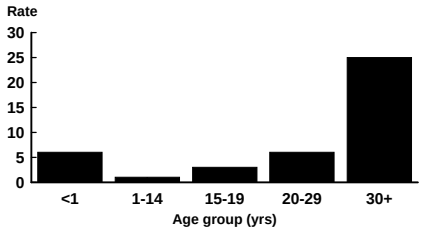
In the pre-vaccine era, approximately 10,000 persons with varicella required hospitalization each year. Hospitalization rates were approximately 2-3 per 1,000 cases among healthy children and 8 per 1,000 cases among adults. Death occurred in approximately 1 in 60,000 cases. From 1990 through 1996, an average of 103 deaths from varicella was reported each year. Most deaths occur in immunologically normal children and adults.

Varicella
Groups at Increased Risk of Complications

- **Normal adults**
- **Immunocompromised persons**
- **Newborns with maternal rash onset within 5 days before to 48 hours after delivery**

The risk of complications from varicella varies with age. Complications are infrequent among healthy children. They are much higher in persons >15 years of age and infants <1 year of age. For instance, among children 1-14 years of age, the fatality rate of varicella is approximately 1 per 100,000 cases. Among persons 15-19 years, the fatality rate is 2.7 per 100,000 cases, and among adults 30-49 years of age, 25.2 per 100,000 cases. Adults account for only 5% of reported cases of varicella, but account for approximately 35% of mortality.

Varicella
Fatality Rate in Healthy Persons



Immunocompromised persons have a high risk of serious varicella infection and a high risk of disseminated disease (up to 36% in one report). These persons may have multiple organ system involvement, and the disease may become fulminant and hemorrhagic. The most frequent complications in immunocompromised persons are pneumonia and encephalitis. Children with HIV infection are at increased risk for morbidity from varicella and herpes zoster.

Perinatal infection

The onset of maternal varicella from 5 days before to 2 days after delivery may result in overwhelming infection of the neonate and a fatality rate as high as 30%. This severe disease is believed to result from fetal exposure to varicella virus without the benefit of passive maternal antibody. Infants born to mothers with onset of maternal varicella 5 days or more prior to delivery

usually have a benign course, presumably due to passive transfer of maternal antibody across the placenta.

Congenital VZV infection

Primary varicella infection in the first 20 weeks of gestation is occasionally associated with a variety of abnormalities in the newborn, including low birth weight, hypoplasia of an extremity, skin scarring, localized muscular atrophy, encephalitis, cortical atrophy, chorioretinitis, and microcephaly. This constellation of abnormalities, collectively known as congenital varicella syndrome, was first recognized in 1947. The risk of congenital abnormalities from primary maternal varicella infection during the first trimester is felt to be very low (<2%). Rare reports of congenital birth defects following maternal zoster exist, but virologic confirmation of maternal lesions is lacking. Intrauterine infection with VZV, particularly after 20 weeks gestation, is associated with zoster in those infants at an earlier age; the exact risk is unknown.

Congenital Varicella Syndrome

- **Results from maternal infection during pregnancy**
- **Period of risk may extend through first 20 weeks of pregnancy**
- **Atrophy of extremity with skin scarring, low birth weight, eye and neurologic abnormalities**
- **Risk appears to be small (<2%)**

Laboratory Diagnosis

Laboratory diagnosis is not routinely required, but is useful if confirmation of the diagnosis or determination of susceptibility is necessary.

While rarely necessary for diagnosis, varicella zoster virus may be isolated in tissue culture. The most frequent source of isolation is vesicular fluid. The virus is difficult to isolate from respiratory secretions.

Stained smears from vesicular scrapings (Tzanck smear) may reveal multinucleated giant cells, consistent with VZV and herpes simplex virus (HSV) infection. In some instances, stains of vesicular scrapings may be tested using a fluorescent monoclonal antibody test which is very sensitive and specific.

A reliable history of chickenpox has been found to be a valid measure of immunity to varicella because the rash is distinctive, and subclinical cases are unusual. As a result, serologic testing of children is generally not necessary. However, **serologic testing** may be useful in adult vaccination programs.

A variety of serologic tests for varicella antibody are available. Available tests include compliment fixation (CF), indirect fluorescent antibody (IFA), fluorescent antibody to membrane antigen (FAMA), neutralization, indirect hemagglutination (IHA), immune adherence hemagglutination (IAHA), radioimmunoassay (RIA), latex

Varicella Laboratory Diagnosis

- **Isolation of varicella virus from clinical specimen**
- **Significant risk in varicella IgG by any standard serologic assay (e.g., enzyme immunoassay)**
- **Positive serologic test for varicella IgM antibody**

agglutination (LA), and enzyme-linked immunosorbent assay (ELISA). IFA, IAHA, FAMA, neutralization, and RIA are sensitive tests, but are time consuming and have requirements that make them unsuitable for general diagnostic laboratories. Compliment fixation (CF) tests have been widely used, but are the least sensitive test. Enzyme linked immunosorbent assay (ELISA) is sensitive and specific, simple to perform, and is widely available commercially. A commercially available latex agglutination (LA) is sensitive, and simple and rapid to perform. LA is generally more sensitive than commercial ELISA tests. Either of these tests would be useful for screening for varicella immunity.

For the diagnosis of acute varicella infection, serologic confirmation would include a significant rise in varicella IgG by any standard serologic assay, or a single positive serologic test for varicella IgM antibody

Varicella Epidemiology

• Reservoir	Human - endemic
• Transmission	Airborne droplet Direct contact with lesions
• Communicability	1-2 days before to 4-5 days after onset of rash May be longer in immunocompromised

Epidemiology

Occurrence

Varicella and herpes zoster occur worldwide. There are data that suggest that varicella infection is less common in childhood in tropical areas, where chickenpox occurs more commonly among adults. The reason(s) for this difference in age distribution are not known with certainty, but may be due to lack of childhood varicella infection in rural populations.

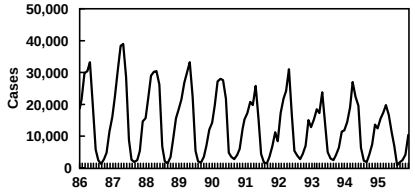
Reservoir

Varicella is a human disease. No animal or insect source or vector is known to exist.

Transmission

Infection with VZV occurs through the respiratory tract. The most common mode of transmission of VZV is believed to be person-to-person from infected respiratory tract secretions. Transmission may also occur by respiratory contact with airborne droplets, or by direct contact or inhalation of aerosols from vesicular fluid of skin lesions of acute varicella or zoster.

Varicella - United States, 1986-1995
Cases by Month of Report



Temporal pattern

In temperate areas, varicella has a distinct seasonal fluctuation, with the highest incidence occurring in winter and early spring. In the United States, incidence is highest between March and May, and lowest between September and November. Less seasonality is reported in

tropical areas. Herpes zoster has no seasonal variation and occurs throughout the year.

Communicability

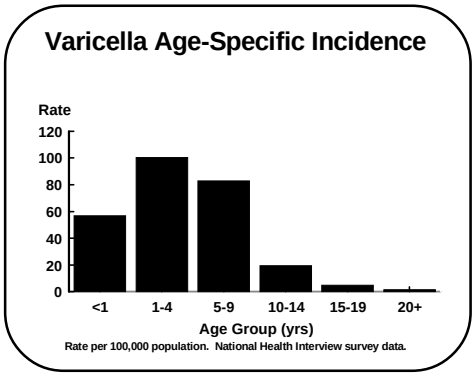
The period of communicability extends from 1 to 2 days before the onset of rash through the first 4 to 5 days, or until lesions have formed crusts. Immunocompromised patients with progressive varicella are probably contagious during the entire period new lesions are appearing. The virus has not been isolated from crusted lesions.

Varicella is highly contagious. It is less contagious than measles, but more so than mumps and rubella. Secondary attack rates among susceptible household contacts of persons with varicella are as high as 90% (that is, 9 out of 10 susceptible household contacts of persons with varicella will become infected).

Secular Trends in the United States

Varicella is endemic in the United States and virtually all persons who are not vaccinated acquire varicella by adulthood. As a result, the number of cases occurring annually without a vaccination program should approximate the birth cohort, or approximately 4 million. Varicella was removed from the list of nationally notifiable conditions in 1991, but some states continue to report cases to CDC. Between 100,000 to 200,000 cases of varicella are reported annually representing 3%-6% of all cases. Incidence is expected to decline as vaccine coverage levels increase.

The majority of cases (approximately 85%) occur among children less than 15 years of age. In the past, the highest age-specific incidence of varicella was among children 5-9 years of age. However, in recent years, the highest incidence has shifted to children 1-4 years of age who account for 39% of all cases. This change in age distribution is probably coincidental with earlier exposure to VZV in preschool and child care settings. Children 5-9 years of age account for 38% of cases. Adults 20 years of age and older account for only 7% of cases (National Health Interview Survey data, 1990-1994).



Herpes zoster

Herpes zoster is not a notifiable condition. An estimated 300,000 episodes of zoster of occur annually. Ninety-five percent of these episodes are first occurrences, and 5% are recurrences. The risk of zoster increases with increasing age. By age 80, almost 15% of persons will have experienced at least one episode of zoster.

Varicella Vaccine

Characteristics

Varicella Vaccine

- **Composition** — **Live virus (Oka-Merck strain)**
- **Efficacy** — **95% (Range, 65%-100%)**
- **Duration of Immunity** — **>7 years**
- **Schedule** — **1 Dose (<13 years of age)**

May be administered simultaneously with measles-mumps-rubella (MMR) vaccine

Varicella zoster vaccine is a live attenuated viral vaccine, derived from the Oka strain of VZV. The vaccine virus was isolated by Takahashi in the early 1970s from vesicular fluid from a healthy child with varicella disease.

Varicella vaccine was licensed for general use in Japan and Korea in 1988. It was licensed in the United States in 1995. The virus was attenuated by sequential passage in human embryonic lung cell culture, embryonic guinea pig fibroblasts, and in WI-38 human diploid cells. The Oka/Merck vaccine has undergone further passage through MRC-5 human diploid cell cultures for a total of 31 passages.

The reconstituted vaccine contains small amounts of sucrose, processed porcine gelatine, sodium chloride, monosodium L-glutamate, sodium diphosphate, potassium phosphate, and potassium chloride, and trace quantities of residual components of MRC-5 cells (DNA and protein), EDTA, neomycin, and fetal bovine serum. The vaccine does not contain egg, ovalbumin, or preservative.

Immunogenicity and vaccine efficacy

After one dose of vaccine, 97% of children 12 months to 12 years of age develop detectable antibody titers. Over 90% of vaccine responders maintain antibody for at least 6 years. In Japanese studies, 97% of children had antibody 7 to 10 years after vaccination. Vaccine efficacy is estimated to be 90% against infection, and 95% against severe disease.

Among healthy adolescents and adults, an average of 78% develop antibody after one dose and 99% develop antibody after a second dose given 4 to 8 weeks later. Antibody has persisted for at least 1 year in 97% of vaccinees after the second dose given 4 to 8 weeks after the first dose. Studies on the persistence of antibody and clinical efficacy in both children and adults are ongoing.

Breakthrough Infection

- **Immunity appears to be longlasting**
- **1% of recipients of current lots per year develop chickenpox**
- **Breakthrough disease much milder than in unvaccinated persons**
- **No evidence that risk of breakthrough infection increases with time since vaccination**

Immunity appears to be long-lasting, and is probably permanent in the majority of vaccinees. However, approximately 1% of vaccinees per year have developed breakthrough infections (*i.e.*, developed varicella disease even though they had responded to the vaccine). All breakthrough infections have been mild, with fewer lesions (generally fewer than 50), many of which are maculopapular rather than vesicular. Most persons with

breakthrough infection do not have fever. There have been no complications. Illness associated with breakthrough infection has not increased in severity during the 7-10 years of follow-up study after vaccination.

Vaccination Schedule and Use

Varicella virus vaccine is recommended for all children without contraindications at 12-18 months of age. The vaccine may be given to all children at this age regardless of prior history of varicella. However, immunization is not necessary in children with reliable histories of chickenpox.

Varicella vaccine is also recommended for immunization of all susceptible children by the 13th birthday. Children who have not been immunized previously and who do not have a reliable history of chickenpox are considered susceptible. Efforts should be made to assure varicella immunity by this age, because after 13 years of age varicella disease is more severe, complications are more frequent, and two doses of vaccine are required.

Varicella Vaccine Recommendations
Children

- **Routine vaccination at 12 to 18 months of age**
- **Recommended for all susceptible children by the 13th birthday**

Varicella vaccine should be administered subcutaneously. It has been shown to be safe and effective in healthy children when administered at the same time as measles-mumps-rubella (MMR) vaccine at separate sites and with separate syringes. If varicella and MMR vaccines are not administered at the same visit, they should be separated by at least 28 days. Varicella vaccine may also be administered simultaneously (but at separate sites with separate syringes) as all other childhood vaccines (DTP/DTaP, *Haemophilus influenzae* type b, hepatitis B, IPV/OPV). The Advisory Committee on Immunization Practices (ACIP) strongly recommends that varicella vaccine be administered simultaneously with all other vaccines recommended at 12 to 18 months of age.

Children with a reliable history of chickenpox can be assumed to be immune to varicella. A parental history is acceptable, and physician documentation is not necessary. Children without a reliable history, or with an uncertain history of chickenpox should be considered susceptible. Serologic testing of such children prior to vaccination is not warranted, because the majority of children between 12 months and 12 years of age without a clinical history of chickenpox are susceptible. Prior history of chickenpox is not a contraindication to varicella vaccination.

Varicella vaccine is approved for **susceptible adolescents and adults.** Approximately 80% of adolescents and adults respond to a single dose of varicella vaccine. In contrast, at least 97% of healthy children will develop detectable antibody after a single dose. As a result, persons 13 years of age and older should receive **two doses** of varicella vaccine separated by 4 to 8 weeks. If there is a lapse of more than 8 weeks after the first dose, the second dose may be administered without repeating the first dose.

Varicella Vaccine Recommendations
Adolescents and Adults

- **Persons ≥13 years of age without history of varicella**
- **Two doses separated by 4 - 8 weeks**
- **Up to 90% of adults immune**
- **Serologic testing may be cost effective**

Adolescents and adults with reliable parental or personal histories of chickenpox can be assumed to be immune. Those without a reliable history can be considered to be susceptible, or may be tested to determine varicella immunity. Epidemiologic and serologic studies indicate that over 90% of adults are immune to varicella. In addition, 71% to 93% of adults without a reliable history of chickenpox are actually immune. As a result, serologic testing prior to vaccination is likely to be cost effective for adults. As with children, a prior history of chickenpox is not a contraindication to varicella vaccination.

Assessment of varicella immunity of all adolescents and adults, and vaccination of those who are susceptible, is desirable to protect these individuals from the higher risk of complications from acquired varicella. Vaccination may be offered at the time of routine health care visits. However, specific assessment efforts should be focused on adolescents and adults who are at highest risk of exposure, and those most likely to transmit varicella to others.

Varicella vaccination should be considered for **susceptible adolescents and adults who are high risk of exposure to varicella.** This group includes persons who live or work in environments in which there is a high likelihood of transmission of varicella, such as teachers of young children, day care workers, and residents and staff in institutional settings; persons who live or work in environments in which varicella transmission may occur (*e.g.* college students, inmates and staff of correctional institutions, and military personnel); nonpregnant women of childbearing age, in order to reduce the risk of VZV transmission to the fetus if the susceptible woman should develop varicella during pregnancy; and international travelers.

Varicella Vaccine Recommendations
Adolescents and Adults

- **Susceptible persons at high risk of exposure or severe illness**
  - **Teachers of young children**
  - **Institutional settings**
  - **Military**
  - **Women of childbearing age**
  - **International travelers**

Varicella vaccination is also recommended for susceptible **adolescents and adults who will have close contact with persons at high risk for serious complications of acquired varicella.** This group would include health care workers and susceptible family contacts of immunocompromised individuals.

The ACIP recommends that **all health care workers** be immune to varicella, either from a reliable history of varicella disease or vaccination. In health care settings, serologic screening of personnel who are uncertain of their varicella history, or who claim not to have had the disease, is likely to be cost effective. Testing for varicella immunity following two doses of vaccine is not considered necessary because 99% of persons are seropositive after the second dose.

Varicella Vaccine Recommendations Adolescents and Adults

- **Susceptible persons likely to expose persons at high risk for severe illness**
  - **Health care workers**
  - **Family members of immuno-compromised persons**

Seroconversion may not always result in full protection against disease (see section on immunogenicity and vaccine efficacy for information on breakthrough infection). If a vaccinated health care worker is exposed to varicella, the exposed person should be tested for varicella antibody as soon as possible following the exposure. Persons with detectable antibody are unlikely to develop varicella. Persons without antibody can be retested 5-6 days later to determine if an anamnestic response is present (*i.e.*, antibody appears quickly after exposure). If antibody is present less than 7 days after exposure it is unlikely that the exposed person will develop disease. Persons who remain susceptible (*i.e.*, antibody negative) 7 days following exposure should be furloughed, or monitored very closely and then furloughed at the onset of symptoms suggestive of varicella.

Vaccination of Health Care Workers

- **Recommended for all susceptible health care workers**
- **Prevaccination serologic screening probably cost effective**
- **Postvaccination testing not necessary or recommended**

The risk of transmission of vaccine virus from a vaccinated person to a susceptible contact appears to be very low (see below), and the benefits of vaccinating susceptible health care workers clearly outweigh this potential risk. Transmission of vaccine virus appears to occur primarily if and when the vaccines develops a vaccine-associated rash. As a safeguard, institutions may wish to consider precautions for personnel who develop a rash following vaccination (*e.g.*, avoidance of contact with persons at high risk of serious complications, such as immunosuppressed persons).

Post-exposure prophylaxis

Data from the United States and Japan in a variety of settings indicate that varicella vaccine is effective in preventing illness or modifying the severity of illness if used within 3 days, and possibly up to 5 days, of exposure. ACIP recommends the vaccine for use in susceptible persons following exposure to varicella. If exposure to varicella does not cause infection, postexposure vaccination should induce protection against subsequent exposure. If the exposure results in infection, there is no evidence that administration of varicella vaccine during the incubation period or prodromal stage of illness

increases the risk for vaccine-associated adverse reactions. Although postexposure use of varicella vaccine has potential applications in hospital settings, pre-exposure vaccination of all susceptible health care workers is the recommended and preferred method for preventing varicella in health care settings.

Varicella Vaccine
Post-exposure Prophylaxis
- **Varicella vaccine is recommended for use in susceptible person after exposure to varicella**
- **70%-100% effective if given within 72 hours of exposure**
- **Not effective if >5 days but will produce immunity if not infected**

Varicella outbreaks in some settings (*e.g.*, child care facilities and schools) can last up to 6 months. Varicella vaccine has been used successfully to control these outbreaks. Varicella vaccine should be used for outbreak control by advising exposed susceptible persons to contact their health care providers for vaccination or by offering vaccination through the health department. Guidelines for varicella outbreak investigation and control are available state health departments and from the National Immunization Program.

Adverse Reactions Following Vaccination

Varicella Vaccine
Adverse Reactions
- **Injection site complaints - 20%**
- **Rash - 3%-4%**
  - **May be maculopapular rather than vesicular**
  - **Average 5 lesions**
- **Systemic reactions uncommon**

The most common adverse reactions following varicella vaccine are **injection site complaints** such as pain, soreness, redness, and swelling. Based on information from the manufacturer's clinical trials of varicella vaccine, local reactions are reported by 19% of children, and by 24% of adolescents and adults (33% following the second dose). These local adverse events are generally mild and self-limited. A varicella-like rash at injection site is reported by 3% of children, and by 1% of adolescents and adults following the second dose. In both circumstances, there has been a median of two lesions. These lesions generally occur within 2 weeks, and are most commonly maculopapular rather than vesicular.

A generalized varicella-like **rash** is reported by 4% to 6% of recipients of varicella vaccine (1% after the second dose in adolescents and adults), with a median of five lesions. Most of these generalized rashes occur within 3 weeks and most are maculopapular.

Zoster Following Vaccination
- **Most cases in children**
- **Risk from wild virus 4 to 5 times higher than from vaccine virus**
- **Mild illness without complications**

Fever within 42 days of vaccination is reported by 15% of children and 10% of adolescents and adults. The majority of these episodes of fever have been attributed to intercurrent illness rather than to the vaccine.

Varicella vaccine is a live virus vaccine, and results in a latent infection, similar to that caused by wild varicella virus. Consequently, **zoster caused by the vaccine virus** has been reported. To date, fewer than 50 reports of zoster in a vaccinated person, mostly children, have been received. Not all these cases have been confirmed as having been caused by vaccine virus. Among children, the

rate of zoster following varicella vaccine is estimated to be 18 cases per 100,000 person-years of observation. This rate is 4-5 times less than the estimated 77 cases per 100,000 person-years of observation for persons infected with wild varicella virus. All cases of zoster following vaccine have been mild and have not been associated with complications, including post-herpetic neuralgia.

Contraindications and Precautions to Vaccination

Contraindications and precautions to varicella vaccine are similar to those for other live attenuated vaccines. Persons with a **severe allergic reaction to a vaccine component or following a prior dose of vaccine** should not receive varicella vaccine. Varicella vaccine contains minute amounts of neomycin and gelatin, but does not contain egg protein or preservatives.

Varicella Vaccine
Contraindications and Precautions

- **Severe allergy to vaccine component or prior dose of vaccine**
- **Pregnancy**
- **Immunosuppression**
- **Moderate or severe acute illness**
- **Recent blood product**

Persons with **immunosuppression** due to leukemia, lymphoma, generalized malignancy, immune deficiency disease, or immunosuppressive therapy should not be vaccinated. However, treatment with low dose (<2 mg/kg/day), alternate day, topical, replacement, or aerosolized steroid preparations is not a contraindication to varicella vaccination. Persons whose immunosuppressive therapy with steroids has been stopped for 1 month (3 months for chemotherapy) may be vaccinated. Varicella vaccine is available from the manufacturer under a research protocol for special use in certain patients with acute lymphoblastic leukemia in remission. Please consult the ACIP statement or contact the manufacturer for further information.

Varicella vaccine should not be administered to persons with cellular immunodeficiency. However, in 1999, ACIP recommended that persons with isolated humoral immunodeficiency (e.g., hypogamma-globulinemia and agamma-globulinemia) should be vaccinated.

Varicella Vaccine
Use in Immunocompromised Persons

- **Most immunocompromised persons should <u>not</u> be vaccinated**
- **Vaccinate persons with humoral immunodeficiency**
- **Consider varicella vaccination for asymptomatic HIV-infected children with CD4% ≥25% (CDC class A1 and N1)**

Persons with moderate or severe cellular immunodeficiency resulting from infection with human immunodeficiency virus (HIV), including persons diagnosed with acquired immune deficiency syndrome (AIDS) should not receive varicella vaccine. However, vaccination should be considered for children with asymptomatic or mildly symptomatic HIV infection (CDC class N1 or A1, age-specific CD4+ T-lymphocyte percentage of >25%). These children should receive two doses of varicella vaccine with a 3 month interval between doses. Because persons with impaired cellular immunity are potentially at greater risk for complications after vaccination with a live vaccine,

these vaccinees should be encouraged to return for evaluation if they experience a postvaccination varicella-like rash.

Women known to be **pregnant** or attempting to become pregnant should not receive varicella vaccine. The effects of varicella vaccine on a developing fetus are unknown. Since infection with wild varicella virus poses only a small risk to the fetus, and the vaccine virus is attenuated, the risk to the fetus, if any, should be even lower. Although the manufacturer's package insert states otherwise, ACIP and the American Academy of Pediatrics recommend that pregnancy be avoided for 1 month following receipt of varicella vaccine.

Varicella Vaccination in Pregnancy Registry

1-800-986-8999

The manufacturer, in collaboration with the Centers for Disease Control and Prevention has established a **Varicella Vaccination in Pregnancy registry** to monitor the maternal-fetal outcomes of pregnant women inadvertently given varicella vaccine. The telephone number for the Registry is 1-800-986-8999.

Vaccination of persons with **moderate or severe acute illnesses** should be postponed until the condition has improved. This precaution is intended to prevent complicating the management of an ill patient with a potential vaccine adverse event, such as fever. Minor illness, such as otitis media and upper respiratory infections, concurrent antibiotic therapy, and exposure or recovery from other illnesses are not contraindications to varicella vaccine. Although there is no evidence that either varicella or varicella vaccine exacerbates tuberculosis, vaccination is not recommended for persons known to have untreated active tuberculosis. Tuberculosis skin testing is not a prerequisite for varicella vaccination.

The effect of the administration of **antibody-containing blood products** (*e.g.*, immune globulin, whole blood or packed red blood cells, intravenous immune globulin, varicella zoster immune globulin [VZIG]) on the response to varicella vaccine virus is unknown. Because of the potential inhibition of the response to varicella vaccination by passively transferred antibodies, varicella vaccine should not be given for at least 5 months after antibody-containing blood products. Immune globulin or VZIG should not be given for 3 weeks following vaccination unless the benefits exceed those of the vaccine. In such cases, the vaccinees should either be revaccinated 5 months later or tested for immunity 6 months later and revaccinated if seronegative.

No adverse events following varicella vaccination related to the use of **salicylates** (*e.g.*, aspirin) have been reported to date. However, the manufacturer recommends that vaccine recipients should avoid the use of salicylates for 6 weeks after receiving varicella vaccine because of the association between aspirin use and Reye syndrome following chickenpox.

Transmission of varicella vaccine virus

Available data suggest that transmission of vaccine virus is a rare event. To date, fewer than 50 instances of suspected secondary transmission of vaccine virus have been reported. However, in only 3 instances has the secondary clinical illness been shown to be caused by vaccine virus. Several other cases of suspected secondary transmission have been determined to have been caused by wild varicella virus. However, in studies of household contacts, several instances of asymptomatic seroconversion have been observed. It appears that transmission occurs mainly, and perhaps only, when the vaccinee develops a rash. If a vaccinated child develops a rash, it is recommended that close contact with persons at high risk of complications of varicella, such as immunocompromised persons, be avoided until the rash has resolved.

Transmission of Vaccine Virus

- **Transmission of vaccine virus rare**
- **Asymptomatic seroconversion may occur in susceptible contacts**
- **Risk of transmission increased if vaccinee develops rash**

Vaccine Storage and Handling

Varicella vaccine is very fragile and must be handled with extreme care. To maintain potency, the lyophilized vaccine must be stored frozen at an average temperature of +5°F (-15°C). Household freezers, including frost-free models, manufactured within the last 5-10 years, are designed to maintain temperatures as low as -4°F (-20°C), and are acceptable for storage of the vaccine. Refrigerators with ice compartments that are not tightly enclosed or are enclosed with unsealed, uninsulated doors (*i.e.*, small dormitory-style refrigerator/freezer combinations) will generally not be capable of maintaining the required storage temperature. Regardless of the type of freezer, providers should check the adequacy of their freezer storage before obtaining vaccine by monitoring and verifying the temperature of their freezer.

Vaccine Storage and Handling

- **Store frozen at -15 C (+5 F) or lower**
- **Generally should not be refrozen**
- **Store diluent at room temperature or refrigerate**
- **Discard if not used within 30 minutes of reconstitution**

The vaccine diluent should be stored separately at room temperature or in the refrigerator. The vaccine should be reconstituted according to the directions in the package insert and only with the diluent supplied, which does not contain preservative or other anti-viral substances that might inactivate the vaccine virus. Once reconstituted, the vaccine must be used immediately to minimize loss of potency. The vaccine must be discarded if not used within 30 minutes of reconstitution.

Varicella Vaccine Information

1 - 800 - 9VARIVAX

If varicella vaccine is inadvertently placed in the refrigerator, or if lyophilized vaccine is left at room temperature for a short time, it may still be potent enough to use. Mishandled vaccine should be clearly marked and replaced in the freezer separate from properly handled vaccine. After storing the vaccine, the manufacturer must be contacted for recommendations before any of the mishandled vaccine is used. The Merck Vaccine Division varicella information telephone number is 800-9VARIVAX (800-982-7482). If the vaccine has been kept cold, or has been exposed to room temperature for a very short time, the manufacturer may recommend that the expiration date be shortened, and that the vaccine be used as quickly as possible. Mishandled vaccine should never be destroyed until the manufacturer has been consulted.

Because of the lability of varicella vaccine, transport of the vaccine from a central clinic or storage area to an off-site clinic will be very difficult. Until more information on the stability of the vaccine at higher-than-recommended temperatures is available, such off-site transport is discouraged. If off-site transport is attempted, a high-quality container should be used, the vaccine should be transported on dry ice, and the temperature should be monitored continuously, to assure that the appropriate storage temperature is maintained.

Varicella Zoster Immune Globulin (VZIG)

VZIG is a human blood product that contains high titers of varicella zoster virus antibody. It was licensed in 1981, and is **available throughout the country from the American Red Cross.** If administered within 96 hours of exposure, VZIG can modify or prevent clinical varicella and prevent complications or death, especially in susceptible immunocompromised individuals.

The decision to administer VZIG should be based on whether the patient is susceptible either by having a negative history of chickenpox or by lacking documentation of vaccination, whether the exposure is likely to result in infection and, most importantly, whether the patient is at greater risk of complications than the general population. VZIG is expensive ($400-$500 for the maximum dose in an adult) and provides only temporary protection.

VZIG is indicated for use in susceptible individuals at high risk for complications who have had a significant exposure (continuous household contact; playmate contact of over an hour; hospital contact in the same 2- to 4-bed room; or prolonged direct contact) to a person with varicella. It is

most commonly used for post-exposure prophylaxis of immunocompromised children (immune deficiencies, neoplastic disease, or on immunosuppressive therapy), and newborns of mothers with varicella onset 5 days before to 48 hours days after delivery. It is also recommended for premature infants with postnatal exposure, including those born at less than 28 weeks gestation or less than 1,000 gram birth weight (who may not have received adequate maternal antibody regardless of whether the mother is immune), or premature infants whose mother is not immune to varicella.

Healthy and immunocompromised adults and pregnant women are at increased risk of complications of varicella. VZIG should be considered if such individuals are considered to be susceptible. There is no evidence that VZIG will prevent congenital varicella if given as post-exposure prophylaxis to a pregnant woman.

Varicella Zoster Immune Globulin (VZIG)

- **May modify or prevent disease if given <96 hours after exposure**
- **Indications**
  - **Immunocompromised persons**
  - **Newborn of mothers with onset 5 days before to 2 days after birth**
  - **Premature infants with postnatal exposure**
  - **Susceptible adults and pregnant women**

VZIG is supplied in vials containing 125 or 625 units. The recommended dose considered likely to prevent or modify varicella is 125 units per 10 kilograms of body weight, up to a maximum of 625 units, or five vials. Higher doses can be considered for immunosuppressed persons. VZIG is given intramuscularly, and must never be given intravenously. It should be given within 96 hours of exposure, preferably as soon as possible. The administration of VZIG may prolong the incubation period of varicella to 28 days or longer post-exposure.

More detailed information on the evaluation of a person exposed to varicella and the use of VZIG may be found in the varicella ACIP statement.

Special Varicella Exposure Situations

Hospital personnel

Susceptible workers with significant exposure to varicella should be relieved from direct patient contact from day 10 to day 21 after exposure. If workers develop chickenpox, varicella lesions must be crusted before they return to direct patient contact. Receipt of VZIG does not change this recommendation for reassignment. Since VZIG can prolong the incubation period, the period of removal from direct patient contact should be lengthened by 1 week or more.

Newborns

Newborn with maternal rash onset 5 days before to 48 hours after delivery should receive VZIG. Since about 50% of infants who receive VZIG will develop varicella, if these infants remain hospitalized beyond age 10 days, they should be kept in strict isolation for the entire incubation period (until day 28 or longer).

Acyclovir

Acyclovir Therapy*

- **Healthy nonpregnant persons ≥13 years of age**
- **Children >12 months with chronic cutaneous or pulmonary disorders or on salicylate therapy**
- **Children receiving short intermittent or aerosolized steroids**
- **IV in immunocompromised children and adults with viral-mediated complications**
- **Not recommended for post-exposure prophylaxis**

***recommended by the American Academy of Pediatrics**

Acyclovir is a synthetic nucleoside analog that inhibits replication of human herpes viruses, including VZV. Intravenous acyclovir has been available since the early 1980s for use in immunocompromised patients with varicella. Oral acyclovir was approved in 1992 for the treatment of chickenpox in otherwise healthy children. Clinical studies indicate that acyclovir may be beneficial if given within 24 hours of onset of rash, resulting in reductions in the number of days new lesions appeared, in the duration of fever, and in the severity of cutaneous and systemic signs and symptoms. Acyclovir has not been shown to decrease transmission of varicella, reduce the duration of absence from school, or reduce complications.

Varicella - Summary

- **Endemic**
- **Most cases among school-age children**
- **Live attenuated vaccine**
- **Coverage level improving steadily**

ACIP has not made recommendations regarding the use of acyclovir. The American Academy of Pediatrics (AAP) does not consider acyclovir in healthy children of sufficient benefit to justify routine administration to normal children. Because complicated varicella and more severe disease may occur in adolescents and adults or secondary cases in the household, AAP considered these appropriate situations for use of the drug. Acyclovir may also be considered for children over 12 months of age with a chronic cutaneous or pulmonary disorder, or on salicylate therapy, and for children receiving short, intermittent or aerosolized courses of corticosteroids. If the child is immunocompromised, intravenous administration is indicated. Corticosteroids should be discontinued, if possible, after exposure.

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